Remarks

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 7-12 and 15-25 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Legal Standard

The test of enablement is whether one of ordinary skill in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988); *In re Stephens,* 529 F.2d 1343, 199 U.S.P.Q. 659 (C.C.P.A. 1976). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 13321, 1332 (Fed. Cir. 1991); *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)).

Whether undue experimentation is needed is not based upon a single factor; it is a conclusion reached by weighing many factors. These factors have been summarized in *In re Wands,* 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) and include, but are not limited to:

(1) The quantity of experimentation necessary (time and expense);

(2) The amount of direction or guidance presented;

(3) The presence or absence of working examples of the invention;

(4) The nature of the invention;

(5) The state of the prior art;

(6) The relative skill of those in the art;

(7) The predictability or unpredictability of the art; and

(8) The breadth of the claims.

The M.P.E.P. explains that "[i]t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others." Thus, a conclusion of nonenablement must be based on the evidence as a whole, as related to each of these factors (see M.P.E.P. § 2164.01 (a)).

The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984). There is no requirement for examples.

Claims 7-12 and 15-25 are enabled

Claims 7-12 and 15-25 were rejected under 35 U.S.C. § 112, first paragraph for not being enabled for (1) *in vivo* methods for targeted recombination in which the triple-helix-forming oligonucleotide (TFO) has a Kd of more than 2×10^{-7} (2) targeted recombination *in vivo* or methods in which targeted recombination produces heritable changes in the genome of an intact animal or human.

(1) Claims 7 and 15 have been amended as the examiner has suggested to further define methods for targeted recombination in which the TFO has a Kd of 2×10^{-7} or less. Therefore, the claims as amended are enabled by the specification.

(2) Claim 15 has been amended to further define the method of claim 7 to produce changes in the genome of an intact human or animal further containing the steps of **injecting** the oligonucleotide into an intact human or animal having a sequence that forms a triple-stranded nucleic acid molecule with the target sequence located in the genome of the intact human or animal, wherein the oligonucleotide binds to the targeted sequence with a Kd of less than or equal to 2×10^{-7}, and mutates the target sequence. The examiner at page 8, lines 3-5 of the office action, states that the specification discloses that in mice (***in vivo***) mutagenesis was observed in liver, skin, kidney, colon, small intestine, and lung cells at a frequency five fold that of background (Example 7). In addition, Example 1 at pages 15-27 describes targeted mutagenesis by TFOs ***in vivo*** of monkey COS cells, patient derived XPA cells, patient-derived XPV cells, and normal human fibroblasts. While, as stated above, no examples are required, the specification clearly enables the method of targeted recombination to produce changes in the genome of an intact human or animal. See also the more recent papers by the applicant that further demonstrate that TFOs can produce inheritable changes in intact animals and animal cells, which, even though these occur at a very low frequency, are sufficient to treat disease. See, for example, Faruqi, et al., Mol. Cell. Biol. 20(3):990-1000 (2000); Seidman and Glazer, J. Clin. Invest. 112(4):487-494 (2003); and Luo, et al.,Proc. Natl. Acad. Sci. USA 97(16):9003-9008 (2000). It is important to note that although the examiner's recognize that delivery is an issue, it

is also established that it is not insurmountable and evidence shows that it is possible to practice the claimed methods.

In contrast to the examiner's statements, the key finding of Wang Mol. Cellular Biol. 15(3):1759-1768, 1767 (1995)) is that the binding affinity of TFO's to the target site as measured *in vitro*, was highly correlated with their **intracellular** activity. This work showed that psoralen-conjugated TFOs transfected into monkey COS cells can induce base pair-specific mutations within the supF mutation reported gene in a simian virus 40 (SV 40) genome in these cells. Chan, J. Biol. Chem. 274:11541-11548 (1999) discloses that tethered donor-TFOs (TD-TFOs) mediate targeted sequence alterations within a SV40 shuttle vector in mammalian cells. They observed successful reversion of the supF target gene after *in vitro* co-incubation of the target vector with the TD-TFOs and also after an ***in vivo*** protocol in which cells already containing the shuttle vector were transfected with the oligonucleotides (p. 11547). Barre Proc. Natl. Acad. Sci. 97: 3084-3088 (2000) discloses at page 8 that the results of their work demonstrate **without ambiguity** that TFOs are capable of modifying an **endogenous** target gene. While Seidman J. Clin. Invest. 112: 487-494 (2003) discloses that there are obstacles to TFO activity, Seidman also describes several ***in vivo*** studies demonstrating the ability of TFOs to induce targeted recombination (p. 490-491). In summary, the specification discloses that in mice (***in vivo***) mutagenesis was observed in liver, skin, kidney, colon, small intestine, and lung cells at a frequency five fold that of background following injection of a TFO (AG30) (Example 7) and discloses targeted mutagenesis by TFOs ***in vivo*** of monkey COS cells, patient derived XPA cells, patient-derived XPV cells, and normal human fibroblasts (Example 1). One does not have to do

breeding studies to show inheritance. Inheritance can be shown by replication of modified cells, wherein the progeny cells also show the modification. See the attached definitions of inheritable ("This is the "internally coded, inheritable information" carried by all living organisms. This stored information is used as a "blueprint" or set of instructions for building and maintaining a living creature. These instructions are found within almost all cells (the "internal" part), they are written in a coded language (the genetic code), they are copied at the time of cell division or reproduction and are passed from one generation to the next ("inheritable"). These instructions are intimately involved with all aspects of the life of a cell or an organism. They control everything from the formation of protein macromolecules, to the regulation of metabolism and synthesis."). Subsequent papers provide further support for the statements and methods described in the application, and evidence that low frequency recombination is sufficient for efficacy. The fact that some experimentation is required does not mean that the claims are not enabled. Therefore, the claims as amended are enabled by the specification.

Rejection Under 35 U.S.C. § 112, second paragraph

A. Claims 7-12 and 15-25 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite for allegedly not defining the steps of providing a single-stranded molecule and providing a donor nucleic acid resulting in targeted recombination. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claim 7 has been amended to further define the method for targeted recombination of a nucleic acid molecule as containing the steps of (1) providing a single-stranded oligonucleotide having a sequence that forms a triple-stranded nucleic acid molecule by **hybridizing** with a

target sequence double-stranded nucleic acid molecule with a Kd of less than or equal to 2 x 10-7, and (2) providing a donor nucleic acid **such that recombination of the donor nucleic acid into the target sequence is induced by triple helix formation between the single-stranded oligonucleotide and the double-stranded nucleic acid molecule**. Support for this amendment can be found in the specification at least at page 7, lines 12-18. Claim 7 as amended defines that the triplex formation between the single-stranded oligonucleotide and the target sequence double-stranded nucleic acid molecule stimulates recombination of a donor nucleic acid into the target sequence. It should be noted that the only steps performed by a person are providing the oligonucleotides and the target. The oligonucleotides by definition hybridize and effect the modification. Therefore, claims 7-12 and 15-25 as amended are not indefinite.

B. Claims 9, 12, and 25 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claims 9, 12, and 25 have been amended to correct antecedent basis. These claims as amended recite a "donor nucleic acid" as recited in the claims upon which claims 9, 12, and 25 depend. Therefore, claims 9, 12, and 25 as amended are not indefinite.

C. Claims 15-24 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claim 15 has been amended to further define the method of claim 7 to produce changes in the genome of an intact human or animal further containing the steps of **administering** the

oligonucleotide into an intact human or animal having a sequence that forms a triple-stranded nucleic acid molecule with the target sequence located in the genome of the intact human or animal, wherein the oligonucleotide binds to the targeted sequence with a Kd of less than or equal to 2×10^{-7}, and mutates the target sequence. Claim 15 as amended defines the relationship between the oligonucleotide of claim 7 and the oligonucleotide of claim 15. Claim 15 as amended clarifies what the oligonucleotide is injected into and refers to the target sequence as recited in claim 7. Finally, claims 15-24 as amended further define the method of targeted recombination as defined by claim 7 by administering the oligonucleotide into an intact human or animal such that the oligonucleotide mutates the target sequence. Therefore, claims 15-24 as amended are not indefinite.

D. Claims 19 and 20 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for use of the term "DNA fragment". Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claims 19 and 20 have been amended to recite the term "donor nucleic acid" as recited in the claims upon which claims 19 and 20 depend. Therefore, claims 19 and 20 are not indefinite.

Priority

The present application is a continuation-in-part of U.S.S.N. 09/411,291 filed on October 4, 1999, which is a divisional of U.S.S.N. 08/476,712 filed on June 7, 1995, page 1, paragraph 1. U.S.S.N. 09/411,291, which issued as U.S. Patent No. 6,303,376 ("the '376 patent"), and U.S.S.N. 08/476,712, which issued as U.S. Patent No. 5,962,426 ("the '426 patent"), provide support under 35 U.S.C. 120 for the claims of the present application.

The discussion that follows refers to the '376 patent. The disclosure of the '376 patent and the '426 patent is the same since the 1999 application which issued as the '376 patent is a divisional of the 1995 application which issued as the '426 patent and contains no new subject matter. (1) The claims define methods of targeted recombination using a TFO in combination with a tethered or unlinked donor nucleic acid. The '376 patent discloses at column 3, lines 1-4 that "the binding of the oligonucleotide to the target region stimulates mutations within or adjacent to the target region using cellular DNA synthesis, **recombination**, and repair mechanisms." The '376 patent also discloses that TFO's are particularly useful as a tool to cause targeted mutagenesis. Those of ordinary skill in the art will recognize that mutagenesis can be caused by **recombination**. Therefore, targeted mutagenesis includes targeted recombination. Furthermore, the '376 patent discloses at column 3, lines 49-56, that TFOs can be used to stimulate recombination of a DNA fragment into a target region, but does not distinguish between whether the DNA fragment is linked or unlinked. However, at column 1 to column 2, the '376 patent discloses methods of use of TFOs alone or linked to reactive moieties. The '376 patent also discloses at column 6, lines 40-58, that TFOs can be used to stimulate recombination of a DNA fragment administered in combination with the TFO into a target region. Furthermore the '376 patent discloses at column 6, lines 31-39, that the TFOs can be used alone or in combination and gives as an example a psoralen-**linked** oligonucleotide. Therefore, the '376 patent discloses that TFOs can be used to stimulate recombination administered in combination with a DNA fragment, the '376 patent discloses that the TFOs can be used alone or in combination, and the '376 patent discloses that TFOs can be linked to reactive moieties. It

would be obvious to one of skill in the art that the DNA fragment could be unlinked or linked to the TFO. Therefore, the claims as amended of the present application are supported by the disclosure of the '376 and '426 patents.

(2) The claims define a TFO with a Kd of 2×10^{-7} or less. Support for these claims can be found in the '376 patent at least at column 5, lines 3-4, and at column 9, lines 25-56, and at Table 1. Therefore, the claims as amended of the present application are supported by the disclosure of the '376 and '426 patents.

(3) The claims further define the method for targeted recombination as defined by claim 7 to produce changes in the genome of an intact human or animal that contains the steps of injecting the oligonucleotide into an intact human or animal that binds to the target sequence and mutates the target sequence. The '376 patent describes methods of producing changes in the genome of a human or animal in the specification at least at column 2, lines 11-59, and at column 2, lines 6-41, respectively. Furthermore, the '376 patent discloses at least at column 5, lines 49-58, that the oligonucleotides are preferably injected into mammals. As mentioned above, the '376 patent discloses at least at column 3, lines 49-56, and again at column 6, lines 40-58, methods in which the TFOs can be used to stimulate homologous recombination of a DNA fragment into a target region. Therefore, the claims of the present application are supported by the disclosures of the '376 and '426 patents.

The present application differs from the earlier filed application primarily by virtue of the **examples**. Example 1, which is found in the '376 and '426 patents as well as the present application, specifically describes targeted mutagenesis by TFOs ***in vivo*** of monkey COS cells,

patient derived XPA cells, patient derived XPV cells, and normal human fibroblasts. The remaining examples, 2 through 8, found only in the present application, support the findings disclosed in example 1. Example 2 describes the ability of TFOs to promote recombination in human cell-free extracts. Examples 3, 4, and 5 describe the role of recombination and repair proteins in the pathway of TFO induced recombination. Example 6 describes targeted mutagenesis by TFOs at genomic sites in somatic cells of adult mice. Example 7 describes heritable changes produced by TFO induced recombination in adult mice. Example 8 describes that induced mutagenesis is specifically brought about through triple-helix formation.

It should also be noted that these examples were submitted in the prosecution of the parent application in the form of a 132 declaration by the applicant, in order to overcome very similar 112 rejections. It was clearly made of record in the prior prosecuted application that the examples were supportive of disclosure; not adding new subject matter.

Therefore, the claims of the present application are supported by the disclosures of the '376 and '426 patents.

Rejections Under 35 U.S.C. § 102 and 103

Claims 7-12, 15-21, 23-25 were rejected under 35 U.S.C. § 102(b) as being anticipated by Chan, et al., ("Chan") J. Biol. Chem. 274: 11541-11548 (1999)). Claim 22 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Chan et al.. Applicants respectfully traverse these rejections to the extent that it is applied to the claims as amended.

As discussed above, the present application is entitled to a priority date of 1995. This application is fully entitled to priority under 35 U.S.C. 120 for the claimed subject matter. Therefore, Chan is not available as prior art.

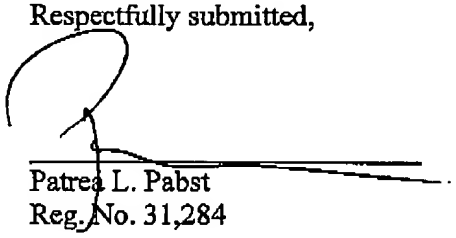
Double Patenting Rejection

Claims 7, 8, 10-12, 15-21, 23, and 24 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 5,776,744 to Glazer et al ("Glazer"). Claims 9, 22, and 25 were rejected under the doctrine of obviousness-type double patenting over claims 1-34 of Glazer in combination with Chan.

U.S. Patent No. 5,776,744 expired on July 8, 2002 for failure to pay the maintenance fee. A copy of the patent bibliographic data as listed by the U.S. P.T.O. is enclosed for your convenience. Therefore, this rejection is moot.

Allowance of claims 7-12 and 15-25 as amended is respectfully solicited.

Respectfully submitted,



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